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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

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24

Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/786,648	WILLIAMS ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50-56* is/are pending in the application.

4a) Of the above claim(s) *54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50-53 and 55-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *22* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

FINAL ACTION

1. This Office Action is responsive to Applicant's amendment and response filed August 14, 2003 and August 21, 2003. Claims 34 and 35 were cancelled and claims 50-55 were added in response to Applicant's amendment filed August 14, 2003. Claims 50-55 were amended and claims 56 was added in response to Applicant's amendment filed August 21, 2003. Claim 54 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. It should be remembered that a restriction requirement and election of species was mailed April 12, 2002. Applicant responded to the restriction requirement and election of species in a response filed May 13, 2003, Applicant's election of Group II with traverse, claims 34-38, species SEQ ID NO:2. This application contains claim 54 drawn to an invention nonelected with traverse in Paper No.11. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

2. The Declaration submitted by Michael Krenicky and Exhibit A (correct copy of PCT Notification Concerning Submission or Transmittal of Priority Document, Form PCT/IB/304 (July 1998) relating to International Applicant No. PCT/GB99/02970) is acknowledged and is sufficient to overcome the objection to foreign priority, page 4, paragraph 5 of the previous Office action.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

Objections and Rejections Withdrawn

4. In view of Applicant's amendment and response, the following Objections are withdrawn:

a) Objection to the specification page 4, paragraph 2 of the previous Office action.

b) Objection to the specification page 4, paragraph 3 of the previous Office action.

c) Rejection of claims 34 and 35 under 35 U.S. C. 112, second paragraph, page 14, paragraph 9 of the previous Office action.

d) Rejection of claim 34 under 35 U.S. C. 112, second paragraph, page 14, paragraph 10 of the previous Office action.

e) Rejection of claim 34 and 35 under 35 U.S. C. 112, first paragraph, pages 5-6, paragraph 6 of the previous Office action.

f) Rejection of claim 34 and 35 under 35 U.S. C. 112, first paragraph, pages 6-10, paragraph 7 of the previous Office action.

g) Rejection of claim 34 and 35 under 35 U.S. C. 112, first paragraph, pages 10-13, paragraph 8 of the previous Office action.

Objection and Rejection Maintained

5. The objection to the drawings is maintained for the reasons set forth on page 4, paragraph 4 of the previous Office Action.

The rejection was on the grounds that the drawings are objected to by the Draftsman under 37 CFR 1.84 or 1.152. See the attached form PTO 948.

Applicant urges that the form PTO 948 was not attached to the previous Office action and therefore they were not able to properly respond to this objection.

A copy of the form PTO 948 is attached to this Office action. However, the objection to the drawings will be maintained until new formal drawings are filed.

6. The rejection under 35 U.S.C. 102(b), is maintained for claims 50-53 and 55-56 for the reasons set forth in pages 14-16, paragraph 11 of the previous Office Action. The Examiner realizes that the newly submitted claims no longer recite variant or homolog language nor do the new claims recite "wherein the peptide does not exhibit GM-1 binding activity". The following rejection is maintained because the newly submitted claims are drawn to a method of treating or preventing autoimmune disease, human T cell leukemia, transplant rejection or graft-versus-host disease, allergy or an infectious disease in subject by administering a peptide which does not differ from the original claims that were drawn to a method of treating a subject having an autoimmune disease, human T cell leukemia, transplant rejection or graft-versus host disease,

allergies or infectious disease comprising administering to the subject an effective amount of a peptide.

The rejection was on the grounds that Williams et al disclose methods for the prevention or treatment of autoimmune disease (claims 3-4, page 44), transplant rejection or graft-versus –host disease (claims 12 and 14 pages 45-46) in which an effective amount of an agent (i.e. a peptide having an effective on GM-1 mediated intracellular signaling events but no GM-1 binding activity). Williams et al also disclose a method for the vaccination of a mammalian subject in which an effective amount of an agent (i.e. a peptide having an effective on GM-1 mediated intracellular signaling events but no GM-1 binding activity) is administered to a subject. Williams et al also disclose that the agents used in vaccinating a mammalian subject can be an agent having an effect on GM-1 binding mediated intracellular signaling events but no GM-1 binding activity (see the Abstract). The amino acid sequence that is the same or similar to SEQ ID NO:2 would be inherent in the teachings of the prior art.

Since the Office does not have the facilities for examining and comparing applicant's peptide with the peptide of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the peptide of the prior art does not possess the same material structural and functional characteristics of the claimed peptide). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant urges that claims 34 and 35 have been cancelled and the rejection is obviated by the amendment. Applicant urges that the new claims are to specific substances not disclosed in the prior art. Applicant urges that a claim is anticipated only if the identical invention is shown in complete detail as contained in the claim. Applicant urges that Williams does not suggest the claimed invention and does not make claims 50-56 obvious.

Applicant's arguments filed August 14, 2003 and August 21, 2003 have been fully considered but they are not persuasive. Newly submitted claims 50-53 and 55-56 are drawn to a method for treating or preventing autoimmune disease, human T-cell leukemia, transplant rejection or graft-host disease, allergy or an infectious disease in a

subject comprising administering to the subject an effective amount of a peptide which (i) comprises the sequence shown in SEQ ID No:2 and (ii) has fewer than 40 amino acids. The claims recite open claim language which means that any amino acid sequence or polypeptide that comprises SEQ ID NO:2 are encompassed by the claims. Williams et al disclose methods for the prevention or treatment of autoimmune disease (claims 3-4, page 44), transplant rejection or graft-versus –host disease (claims 12 and 14 pages 45-46) in which an effective amount of a specific agent (i.e. a peptide) is administered to a subject. The amino acid sequence that is the same as SEQ ID NO:2 would be inherent in the teachings of the prior art. There is nothing on the record to show that the peptides disclosed by Williams are any different from the claimed peptides. Applicant has provided no side-by-side comparison to show that the methods of the prior art differ from that of the claimed methods. Therefore, Williams et al, anticipate the claimed invention.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 50-53 and 55-56 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the

application was field, had possession of the claimed invention. *This is a written description rejection.*

Claims 50-53 and 55-56 are drawn a method for treating or preventing autoimmune disease, human T-cell leukemia, transplant rejection or graft-versus-host disease, allergy or an infectious disease in a subject comprising administering to the subject an effective amount of a peptide which: (i) comprises the sequence shown as SEQ ID NO:2 and had fewer than 40 amino acids. The specification and the claims do not indicate what distinguishing attributes are shared by the members of the genus. Thus, the scope of the claims include numerous structural variants and the genus is highly variant because a significant number of structural differences between genus members are permitted. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO:2 alone is insufficient to describe the genus. Thus, Applicant's have not described a function which is shared by the SEQ ID NO:2 which would adequately describe the claimed genus. One skilled in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the claimed genus. In other words, the claims recite open claim language, which means that any amino acid sequence or polypeptide can comprise SEQ ID NO: 2. The instant specification has not described these polypeptides. The instant specification is only enabled for SEQ ID NO:2. Therefore one of skill in the art could not reasonably conclude that Applicant was in possession of the claimed genus at the time of filing.

Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The protein itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co., Lts.*, 18 USPQ 2d 1016.

Applicant is directed to the *Revised Interium Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement*, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday, December 21, 1999.

As a suggestion, amendment of claims to recite "...consisting of the sequence shown as SEQ ID NO:2 would be sufficient to overcome this rejection.

8. Claims 50-53 and 55-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO:2, does not reasonably provide enablement for all peptides that comprise SEQ ID NO:2 and have less than 40 amino acids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to a method of treating a subject having an autoimmune disease, human T cell leukemia, transplant rejection or graft-versus host disease, allergies or infectious disease comprising administering to the subject an effective amount of a peptide which: (i) comprises SEQ ID NO: 2 and (ii) has fewer than 40 amino acids.

The specification is enabling only for the peptide of SEQ ID NO: 2. There is no guidance provided as to which amino acids can be modified in the polypeptide

comprising SEQ ID NO:2 and still have the peptide retain its biological function. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of peptides broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the peptide determines its structural and functional properties, predictability of which changes can be tolerated in a peptide's amino acid sequence and still retain similar activity requires a knowledge with regard to which amino acids in the peptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the peptide's structure relates to function. However, the problem of the prediction of peptide's structure from mere sequence data of a single peptide and in turn utilizing predicted structural determinations to ascertain functional aspects of the peptide and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple substitutions or multiple modifications of other types and the positions within the peptide's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any peptide and the result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modifications, e.g., multiple substitutions. The sequence of some peptide is highly conserved and one

skilled in the art would not expect tolerance to any amino acid modification in such peptide.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting other peptides having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use peptides that comprise SEQ ID NO: 2 in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

The Applicant has not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any modification of any polypeptide that comprises SEQ ID NO:2. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without

such guidance, the changes which can be made in the peptide's structure and still maintain activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly, extensive and undue. See Amgen Inc v Chugai Pharmaceutical Co Ltd. 927 F 2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Exparte Forman, 230 U.S. P.Q. 546(Bd. Pat=. App & int. 1986).

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention commensurate in scope with the claims.

9. Claims 50-53 and 55-56 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of treating a subject having an autoimmune disease, human T cell leukemia, transplant rejection or graft-versus host disease, allergies or infectious disease comprising administering to the subject an effective amount of a peptide which (i) comprises SEQ ID NO: 2 and (ii) has fewer than 40 amino acids.

The specification has not enabled a method of treating a subject having an autoimmune disease, human T cell leukemia, transplant rejection or graft-verses host disease, allergies or infectious disease comprising administering to the subject an

effective amount of a peptide which: (i) comprises SEQ ID NO: 2 and (ii) has fewer than 40 amino acids. The specification has failed to provide data that show results from studies in which compositions comprising an effective amount of SEQ ID NO: 2 have been administered to a subject thereby protecting any animal's immune system. There are no data disclosed in the instant specification that shows that administering the SEQ ID NO:2 or a polypeptide comprising SEQ ID NO:2 would provide protection against autoimmune disease, human T cell leukemia, transplant rejection or graft-versus host disease, allergies or any infectious disease. The specification has not made a correlation between immunomodulation and autoimmune disease, human T cell leukemia, transplant rejection or graft-verses host disease, allergies or infectious disease.

Nashar et al *(Proc. Natl. Acad. Sci, USA, Vol. 93. p. 226-230)* teach that the ability of toxoids to act as potential carrier for antigen is directly related to their ability to bind ganglioside receptors (page 230). It should be noted that Example 3 of the specification teaches that intranasal immunization with wild type EtxB serum induced a high antibody level and in contrast, EtxB(H57S) (an EtxB mutant) induced a significantly lower antibody response in comparison to wild type EtxB (page 43). Truitt et al, *(Infection and Immunity, April 1998, p. 1299-1308)* teach that novel agents that bind and modulate the function of immune cells are of interest for transplantation immunology, autoimmune disease, vaccine development and other related fields (page 1299, 1st column). Truitt et al teach that bacterial enterotoxins which bind to membrane glycosphingolipids (i.e. gangliosides) on lymphocytes may be useful as

immunomodulatory agents to prevent or modulate T cell mediated disorders (page 1299, 1st column). Truitt et al teach that previous studies have shown that bacterial enterotoxins is significant to prevent Graft-Versus-Host Disease (GVHD) following allogenic bone marrow transplantation in mice, however whether induction of apoptosis or immune deviation or both contribute to decreased GVHD is unclear at present (page 1307, column 2).

It has been recognized by the previously cited art that the mechanism by which enterotoxins bind to receptors result in poor stimulatory and strong inhibitory properties on CD8+ T cells in regard to autoimmune disease is not well understood in the art and it is also recognized in the art and supported by the specification that enterotoxin (EtxB) mutants do not cause apoptosis of CD8+ T cells, however, EtxB mutants show reduced antibody titers after oral and subcutaneous administration. One skilled in the would require guidance in order to make and use the claimed invention in regard to preventing and treating autoimmune diseases with a peptide that comprises SEQ ID NO:2 and has fewer than 40 amino acids. The claimed invention also broadly encompasses the treatment of any infectious disease caused by any microorganism or any allergy caused by an agent. The specification has not provided enablement for a peptide that treats any infectious disease or any allergy since the instant specification does not make a correlation between the use of the claimed peptide and treatment of patients having infectious diseases or allergies. The instant specification does not disclose a peptide comprising SEQ ID NO: 2 and has fewer than 40 amino acids that is use as a pharmaceutical composition for the treatment or prevention of autoimmune disease,

human T cell leukemia, transplant rejection or graft-versus host disease, allergies or infectious disease. One skilled in the art would require guidance in order to make and use the claimed invention in regard to preventing and treating any infectious disease or any allergy. The skilled artisan could not conclude that the amino acid sequence of as set forth in SEQ ID NO:2 can be effective in promoting a protective response, in any host, against autoimmune disease, human T cell leukemia, transplant rejection or graft-versus host disease, allergies or infectious disease. The specification fails to teach how to make and use the claimed invention. The specification is devoid of data to support ability of the claimed SEQ ID NO:2 to protection against autoimmune disease, human T cell leukemia, transplant rejection or graft-versus host disease, allergies or infectious disease. This demonstration is necessary to enable the use of the claimed method. The specification only discloses proliferation bioassays for binding and teaches that SEQ ID NO: 2 possesses immunomodulatory properties (see Example 5). The skilled artisan cannot conclude that a protective immune response can be achieved administering to a subject an effective amount of a peptide which comprises the sequence shown as SEQ ID NO:2 and has few than 40 amino acids with the information provided in the specification. An undue amount of experimentation would be necessary to use the claimed invention by using the limited information disclosed in the specification. Therefore, the specification fails to teach how to make and use the claimed peptides to be used for its intended purpose to treat or prevent autoimmune disease, human T-cell leukemia, transplant rejection or graft-versus-host disease, allergy or an infectious disease in a subject.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Despite the knowledge in the art regarding treating or preventing autoimmune disease, human T-cell leukemia, transplant rejection or graft-versus-host disease, allergy or an infectious disease, the specification has not shown how to use the disclosed peptides in the claimed method of treating. The specification has not shown how to use the claimed peptides to protect a subject having autoimmune disease, human T-cell leukemia, transplant rejection or graft-versus-host disease, allergy or an infectious disease. The specification has not provided data that shows an actual enhancement of a host's immune system in an *in vivo* model. It is determined that there is limited guidance provided in the specification as to how to use the claimed invention and that it would require undue experimentation by the skilled artisan to use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 51 is rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 51 recites "further characterized as a part of "? It is unclear as to what Applicant is referring? What constitutes a part? Clarification is required.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
January 8, 2004

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